REMARKS

By the present amendment, applicants have canceled Claims 11-13. In addition, applicants have amended the independent claims (Claims 1 and 21) to specify that the hydroxypropyl cellulose is low-substituted hydroxypropyl cellulose. Therefore, the claims remaining for consideration by the Examiner are Claims 1-10 and 14-21.

The Examiner has rejected Claims 1-21 under 35 U.S.C. 103(a) as being unpatentable over Harris et al. (U.S. Patent No. 4,743,450) in view of Vivilecchia et al. U.S. Patent No. 6,300,361), the *Handbook of Pharmaceutical Excipients*, Applicants' acknowledgment at page 4, third full paragraph – page 5, second full paragraph of the present specification, and Remington's Pharmaceutical Sciences.

Harris teaches compositions containing an ACE inhibitor, an alkali or alkaline earth metal carbonate such as magnesium carbonate, and a saccharide such as lactose. Harris states in column 3, lines 61-65, that optional excipients may be used in the compositions. In column 4, lines 3-10, Harris lists suitable disintegrating agents as modified starch, polyvinyl pyrrolidone, and modified cellulose derivatives. However, Harris does not teach or suggest low-substituted hydroxypropyl cellulose. In addition, none of Harris' examples use a low-substituted hydroxypropyl cellulose.

Vivilecchia teaches compositions containing an ACE inhibitor and a hydrochloric acid donor. Vivilecchia states in column 2, lines 23-34, that the advantages of the invention is made possible by a select group of hydrochloric acid donors which release hydrochloric acid resulting in greater diffusion through the dosage form matrix as compared to previously used acids.

Vivilecchia lists suitable disintegrates, in column 5, lines 38-40, as microcrystalline cellulose, cross-linked polyvinyl pyrrolidone, and alginic acid. However, Vivilecchia does not teach or suggest low-substituted hydroxypropyl cellulose. In addition, none of the examples in Vivilecchia use a low-substituted hydroxypropyl cellulose.

The *Handbook of Pharmaceutical Excipients*, Fourth Edition, Rowe, Sheskey, and Weller, (2003), has separate chapters for hydroxypropyl cellulose and low-substituted hydroxypropyl cellulose. As stated in the *Handbook of Pharmaceutical Excipients*, on page 294, the low-substituted hydroxypropyl cellulose when dried at 105 °C for 1 hour contains not less than 5% and not more than 16% of hydroxypropoxy groups. In contrast, hydroxypropyl cellulose is defined by a molecular weight range of 50,000 to 1,250,000 according to the *Handbook of Pharmaceutical Excipients*, page 289. Thus, the low-substituted hydroxypropyl cellulose is clearly distinguishable from hydroxypropyl cellulose.

As noted by the Examiner, Remington's Pharmaceutical Sciences teaches a wet granulation method which involves mixing ingredients to form a premix; forming a wet granulation by adding a solvent; drying the wet granulation; milling the resulting dried granulation; and then forming a composition therefrom.

Applicants unexpectedly determined that tablets prepared with an ACE inhibitor, such as quinapril, and a low-substituted hydroxypropyl cellulose exhibited greater stability as determined by the amount of by-products, quinaprilate and DKP, which were formed, as compared to tablets prepared without a low-substituted hydroxypropyl cellulose. Obviously, the lower the amount of by-products which are formed in a particular formulation, the more stable the formulation.

In applicants' Examples 1-4, applicants prepared tablet formulations containing 40 mg of quinapril and different amounts of low-substituted hydroxypropyl cellulose. In Example 1, 136.67 mg of low-substituted hydroxypropyl cellulose was used. In Example 2, no low-substituted hydroxypropyl cellulose was used, and 136.67 mg of microcrystalline cellulose, a filler, was used. In Example 3, 68.33 mg of low-substituted hydroxypropyl cellulose, and 68.34 mg of microcrystalline cellulose were used. In Example 4, 36.67 mg of low-substituted hydroxypropyl cellulose, and 100 mg of microcrystalline cellulose were used.

Applicants' Table 1 on page 10 of the specification sets forth the amount of degradation products formed at 40 °C and 75% relative humidity for each of the tablet formulations prepared in Examples 1-4. The results in Table 1 clearly show that the tablets prepared with low-substituted hydroxypropyl cellulose (Examples 1, 3-4) contained significantly less quinaprilate, as compared to tablets prepared without low-substituted hydroxypropyl cellulose (Example 2).

The combination of Harris, Vivilecchia, the *Handbook of Pharmaceutical Excipients*, and Remington's Pharmaceutical Sciences, therefore, does not place one skilled in the art in possession of applicants' invention as claimed because neither of the references teach a composition containing an ACE inhibitor and a low-substituted hydroxypropyl cellulose, as claimed by applicants.

Applicants respectfully request the Examiner to enter applicants' amendment and pass the application to issuance.

Respectfully submitted,

John D. Thallemer
Attorney for Applicants
Reg. No. 34,940

Novartis
Corporate Intellectual Property
One Health Plaza, Building 430
East Hanover, NJ 07936-1080
(862) 778-7945
Date: July 2, 2004